

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Ognyanov et al. :
Appln. No.: Not Assigned :
Filing Date: Herewith :
For: **Pharmaceutical for Treatment of** : **PRELIMINARY AMENDMENT**
Neurological and :
Neuropsychiatric Disorders :
Reference: 317743-103B :

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Art Unit: 1624 :
Examiner: Colman, B. :
:

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Washington, DC 20231

Prior to examination on the merits, Applicant respectfully requests entry of the following amendments. The amendments are directed to portions of Applicants' invention defined by Group II of the restriction requirement dated June 1, 1998. That restriction requirement set forth groups that in total do not appear to encompass the subject matter that Applicants regard as the invention. Accordingly, some adjustment is needed. As mentioned in Applicants' previous response, Applicants respectfully submit that the prior restriction is too severe, and unjustified by

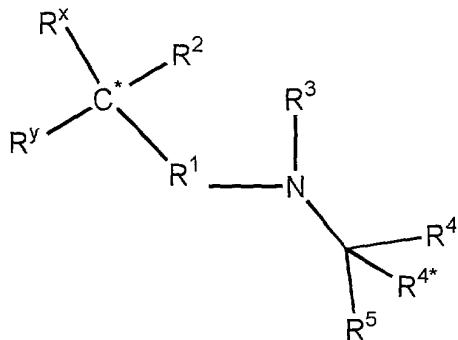
any burden on the examination. Nonetheless, Applicants here submit claims of a reasonable scope for examination.

The claims are framed on the terminology agreed to in the parent case, with such adjustment as needed to reflect the focus on S and O-containing heterocycles linked to C*. The areas where adjustments were made in lead claim 43 are highlighted in the Appendix, as are one additional claim with such an adjustment, and two claims that do not have an analog in the parent case.

IN THE CLAIMS:

Please cancel claims 1-41, and enter new claims 43-74, set forth below:

-- 43. A compound of the following formula:



or a pharmaceutically acceptable salt thereof,

wherein:

- (1) C* is a substituted carbon;
- (2) R² (a) is hydrogen, (C1-C6) alkyl, (C1-C6) alkoxy, cyano, (C2-C7) alkanoyl, aminocarbonyl, (C1-C6) alkylaminocarbonyl, or dialkylaminocarbonyl wherein each alkyl is independently C1 to C6, (b) comprises (where R¹ is not aminoethylene, -O-R⁸ or -S-R^{8*}) hydroxy, fluoro, chloro, bromo or (C2-C7) alkanoyloxy, (c) forms a double bond with an adjacent carbon or nitrogen from one of either R¹, R^xb or R^yb, (d) is R²a linked by R²b to C*, or (e) is ethylene forming a third bridging structure as set forth in (2ⁱⁱⁱ)(b)(i);
- (2ⁱ) R^x is R^xa linked by R^xb to C*;

- (2ⁱⁱ) RY is Ry^a linked by Ry^b to C*;
- (2ⁱⁱⁱ) Rx^a and Ry^a, are independently Ar, which is phenyl or naphthyl, heteroaryl, or or a 5 to 7-membered non-aromatic ring having from 0 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and R^{2a}, when present, is Ar, and wherein:
- (a) heteroaryl comprises thienyl, furanyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, or one of the foregoing fused to phenyl, or methylenedioxyphenyl,
 - (b) each of Rx^a and Ry^a can be independently substituted with one of R^q, R^rO- or R^sS-, wherein each of R^q, R^r and R^s are independently Ar, heteroaryl, adamantyl, or a 5 to 7-membered non-aromatic ring having from 0 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and
 - (c) Rx^a, Ry^a, R^{2a}, R^q, R^r and R^s can be substituted or additionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, bromo, nitro, hydroxy, cyano, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C12) alkyl, (C2-C12) alkenyl, amino, (C1-C6) alkylamino, dialkylamino wherein each alkyl of dialkylamino is independently C1 to C6, (C1-C6) alkoxy, (C2-C7) alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7) alkyloxycarbonyl, aminocarbonyl that can be substituted for hydrogen with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, or amidino wherein the amidino can be independently substituted with up to three (C1-C6) alkyl groups, wherein:
- (i.) the substitutions of Rx^a and Ry^a can be combined to form a second bridge between Rx^a and Ry^a comprising (1) methylene or ethylene, which methylene or ethylene can be substituted by an R² when R² is ethylene to form the third bridging structure, or (2) -CH=CH-, or (3) sulfur, or (4) oxygen, or wherein Rx^a and Ry^a can be directly linked by a single bond,
- (d) wherein at least one of Rx^a, Ry^a, R^q, R^r or R^s is heteroaryl, or a second bridge between Rx^a and Ry^a comprises sulfur or oxygen as set forth below, or Ar substituted with a methylenedioxy;

- (2^{iv}) R^{xb} and R^{2b} are independently a single bond or (C1-C2) alkylene;
- (2^v) R^{yb} is a single bond, oxy, (C1-C2) alkylene, ethenylene or -CH= (where the double bond is with C*), thio, methyleneoxy or methylenethio, or either -N(R^6) or -CH₂-N(R^{6*})-, wherein R^6 and R^{6*} are hydrogen or (C1-C6) alkyl;
- (3) R^1 comprises: a straight-chained (C2-C3) aliphatic group; =N-O-(ethylene), wherein the unmatched double bond is linked to C*; -O-R⁸ or -S-R^{8*} wherein R⁸ or R^{8*} is a ethylene or ethenylene and O or S is bonded to C*; aminoethylene where the amino is bonded to C*;
wherein R^1 can be substituted with up to one hydroxy, up to one (C1-C6) alkoxy or up to one (C2-C7) alkanoyloxy, with up to two independent (C1-C6) alkyl, with up to one oxo, up to one (C1-C6) alkylidene, with the proviso that the hydroxy, alkoxy, alkanoyloxy or oxo substituents are not bonded to a carbon that is bonded to a nitrogen or oxygen;
wherein if R^1 contributes a heteroatom linked to C*, then R^{yb} does not contribute a heteroatom linked to C*; and
wherein the alkyl or alkylidene substituents of R^1 can be linked to form a 3 to 7-membered non-aromatic ring;
- (4) R^3 (a) is hydrogen, (C1-C6) alkyl, or phenyl or phenylalkyl wherein the alkyl is C1 to C6 and the phenyl or phenyl of phenylalkyl can be substituted with the same substituents defined above for the phenyl of R^{xa} , (b) is -R¹²C(R^{xx})(R^{yy})(R^{11}), wherein R¹² is bonded to N, R^{xx} is independently the same as R^x , R^{yy} is independently the same as R^y , R^{11} is independently the same as R^2 and R¹² is independently the same as R^1 ;
- (5) R^4 and R^{4*} are independently hydrogen or (C1-C6) alkyl, or one of R^4 and R^{4*} can be (C1-C6) hydroxyalkyl; and
- (6) R^5 is (CO)NR¹³R¹⁴, (CO)OR¹⁵, (CO)SR¹⁶, (SO₂)NR¹⁷R¹⁸, (PO)(OR¹⁹)(OR²⁰), (CR²²)(OR²³)(OR²⁴), CN or tetrazol-5-yl, wherein (a) R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ R¹⁹ and R²⁰ are independently hydrogen, (C1-C8) alkyl which can include a (C3-C8) cycloalkyl, wherein the carbon linked to the oxygen of R¹⁵ or the sulfur of R¹⁶ has no more than secondary

branching, (C2-C6) hydroxyalkyl, aminoalkyl where the alkyl is C2 to C6 and the amino can be substituted with up to two independent (C1-C6) alkyls, Ar-alkyl wherein the alkyl is C1-C6, or Ar, and (b) R²² is hydrogen or OR²⁵ and R²³, R²⁴ and R²⁵ are independently (C1-C6) alkyl, phenyl, benzyl or acetyl or, the alkyls of R²³ and R²⁴ can be combined to include 1,3-dioxolane or 1,3-dioxane:

wherein the phenyl or naphthyl groups of R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²², R²³ or R²⁴ can be substituted with substituents selected from the group consisting of fluoro, chloro, bromo, nitro, cyano, hydroxy, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C6) alkyl, (C2-C6) alkenyl, (C1-C6) alkylamine, dialkylamine wherein each alkyl is independently C1 to C6, amino, (C1-C6) alkoxy, (C2-C7) alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7) alkyloxycarbonyl, aminocarbonyl that can be N-substituted with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, or amidino that can substituted with up to three (C1-C6) alkyl;

wherein R¹³ and R¹⁴ together with the attached nitrogen can form a 5 to 7-membered ring.

-- 44. The compound of claim 43, wherein at least one of R^{x_a}, R^{y_a}, R^q, R^r and R^s is thienyl or furanyl.

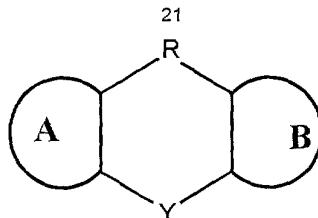
-- 45. The compound of claim 43, wherein at least one of R^{x_a} and R^{y_a} is thienyl or furanyl.

-- 46. The compound of claim 43, wherein (A) at least one of R^{x_a}, R^{y_a} and R^{2_a} is substituted with fluoro, chloro, bromo, hydroxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or (C3-C8) alkyl, (B) at least one of R^{x_a} and R^{y_a} is substituted with R^q, R^rO- or R^sS-, (B) R³ is hydrogen, (C1-C6) alkyl, or phenyl or phenylalkyl wherein the alkyl is C1 to C6 and either such phenyl can be substituted with the same substituents defined above for the phenyl of R^{x_a} or (C) the ring

structures of R^{xa} , R^{ya} and R^{2a} , including substituents thereto, otherwise include at least two aromatic ring structures that together include from 15 to 20 ring atoms.

- 47. The compound of claim 46, wherein at least one of R^{xa} , R^{ya} , R^q , R^r and R^s is substituted with fluoro, trifluoromethyl, trifluoromethoxy, nitro, cyano, or (C₃-C₈) alkyl.
- 48. The compound of claim 43, wherein at least one of R^{xa} and R^{ya} is substituted with R^q , R^rO^- , or R^sS^- .
- 49. The compound of claim 43, wherein an Ar of at least one of R^{xa} , R^{ya} and R^{2a} is phenyl.
- 50. The compound of claim 43, wherein R^{yb} is oxy, methyleneoxy, thio, or methylenethio.
- 51. The compound of claim 50, wherein R^{yb} is oxy or thio.
- 52. The compound of claim 43, wherein R^5 is (CO)NR¹³R¹⁴, (CO)OR¹⁵ or (CO)SR¹⁶.
- 53. The compound of claim 52, wherein R^5 is (CO)OR¹⁵ and R^{15} is (C₂-C₆) alkyl, (C₂-C₄) hydroxyalkyl, phenyl, phenylalkyl wherein the alkyl is C₁-C₃, or aminoalkyl where the alkyl is C₂-C₆ and the amino can be substituted with up to two independent (C₁-C₃) alkyls, wherein the phenyl or the phenyl of phenylalkyl can be substituted.
- 54. The compound of claim 52, wherein R^5 is (CO)OR¹⁵ and R^{15} is hydrogen.
- 55. The compound of claim 43, wherein R^4 is hydrogen, methyl or hydroxymethyl and R^{4*} is hydrogen.
- 56. The compound of claim 43, wherein R^1 is -0-R⁸ or -S-R^{8*}.

-- 57. The compound of claim 56, wherein R^{xa} - R^{xb} , R^{ya} - R^{yb} , and C^* form:



wherein A and B are Ar ring structures consistent with the definitions of R^{xa} and R^{ya} , respectively, and Y is C^* wherein R^{21} either (i.) completes a single bond linking two Ar rings of R^{xa} and R^{ya} , or (ii.) is (C1-C2) alkylene or -CH=CH-, and wherein R^{xa} and R^{ya} can be substituted.

-- 58. The compound of claim 57, wherein R^{21} is CH_2CH_2 or $CH=CH$.

-- 59. The compound of claim 43, wherein R^{xa} and R^{ya} together can be substituted with up to six substituents, R^{2a} , R^q , R^r and R^s can each be substituted with up to 3 substituents, and wherein the presence of each of R^q , R^rO^- or R^sS^- is considered a substitution to the respective ring structure of R^{xa} and R^{ya} .

-- 60. The compound of claim 43, wherein a phenyl of R^3 is substituted with up to three substituents.

-- 61. The compound of claim 43, wherein the Ar of R^{13} , R^{14} , R^{15} , R^{16} R^{17} , R^{18} R^{19} or R^{20} is substituted with up to three substituents.

-- 62. The compound of claim 43, wherein R^3 is hydrogen, (C1-C6) alkyl, or phenyl or phenylalkyl wherein the alkyl is C1 to C6 and the phenyl or phenyl of phenylalkyl can be substituted with the same substituents defined above for the phenyl of R^{xa} .

-- 63. The compound of claim 43, wherein the compound is an optically pure enantiomer.

-- 64. A pharmaceutical composition comprising the compound of claim 43 and a pharmaceutically acceptable excipient.

-- 65. The pharmaceutical composition of claim 64, wherein the compound is present in an effective amount for:

- (1) treating schizophrenia,
- (2) treating epilepsy,
- (3) treating spasticity,
- (4) treating muscle spasm,
- (5) treating pain,
- (6) treating mood disorders,
- (7) enhancing memory or learning, or
- (8) treating learning disorders.

66. The compound of claim 43 wherein:

- (1) R² is hydrogen,
- (2) R^{xa} and R^{ya} are phenyl, thienyl or furanyl, and can be substituted,
- (3) R^{xb} is a single bond and R^{yb} is a single bond or oxy, and
- (4) R⁵ is (CO)NR¹³R¹⁴ or (CO)OR¹⁵, wherein R¹³, R¹⁴, and R¹⁵ are independently hydrogen; (C1-C8) alkyl which can include a (C3-C8) cycloalkyl, wherein the carbon linked to the oxygen of OR¹⁵ has no more than secondary branching; (C2-C6) hydroxyalkyl or aminoalkyl where the alkyl is C2 to C6 and the amino can be substituted with up to two independent (C1-C6) alkyl or phenylalkyl, wherein the alkyl is C1-C6 and the phenyl can be substituted with substituents selected from the group consisting of fluoro, chloro, bromo, nitro, cyano, hydroxy, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C6) alkyl, (C2-C6) alkenyl, (C1-C6) alkylamine, dialkylamine wherein each

alkyl is independently C1 to C6, amino, (C1-C6) alkoxy, (C2-C7) alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7) alkyloxycarbonyl, aminocarbonyl that can be N-substituted with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, amidino that can substituted with up to three (C1-C6) alkyl.

- 67. The compound of claim 66, wherein R² forms a double bond with an adjacent carbon from R¹.
- 68. A method of (1) treating schizophrenia comprising administering a schizophrenia treating effective amount of a compound, (2) of treating epilepsy comprising administering an epilepsy treating effective amount of a compound, (3) treating spasticity comprising administering a spasticity treating effective amount of a compound, (4) treating muscle spasm comprising administering a muscle spasm treating effective amount of a compound, (5) treating pain comprising administering a pain treating effective amount of a compound, (6) treating mood disorders comprising administering a mood disorder treating effective amount of a compound, (7) enhancing memory or learning comprising administering a memory or learning enhancing effective amount of a compound, or (8) treating learning disorders, comprising administering an amount effective for said treating or enhancing of a compound of claim 43.
- 69. The method of claim 68, wherein the spasticity is associated with epilepsy, stroke, head trauma, multiple sclerosis, spinal cord injury or dystonia.
- 70. The method of claim 68 of (1) treating schizophrenia comprising administering a schizophrenia treating effective amount of a compound, (5) treating pain comprising administering a pain treating effective amount of a compound or (6) treating mood disorders comprising administering a mood disorder treating effective amount of a compound.
- 71. The method of claim 68 of treating schizophrenia comprising administering a schizophrenia treating effective amount of the compound.

-- 72. The pharmaceutical composition of claim 65, wherein the compound is present in an effective amount for treating schizophrenia.

-- 73. The compound of claim 43, wherein R¹ is a straight-chained (C2-C3) aliphatic group.

-- 74. The compound of claim 73, wherein R² forms a double bond with an adjacent carbon from R¹.

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R E M A R K S

Entry of the amendment prior to calculation of claim fees is respectfully requested. By the present amendment, claims 42-74 are in the application, for a total of 33 claims, of which two are independent.

Conclusion

Prompt examination on the merits is earnestly solicited.¹

Respectfully submitted,



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